or

$$R^{2b}$$
 $R^{2a}$ 
 $R^{2b}$ 
 $R^{2c}$ 
 $R^{2c}$ 

--3. (Amended) The method as defined in Claim 34 wherein the compound employed has the structure

$$R^{2a}$$
 $R^{2b}$ 
 $R$ 

--4. (Amended) The method as defined in Claim 34 wherein the compound employed has the structure

$$(CH_2)_x CO_2R^4$$

$$R^1$$

$$(CH_2)_m CO_2R^4$$
or

$$(CH_2)_m (CH_2)_m co_2 R^4$$

$$R^2$$

$$R^3$$

--5. (Amended) The method as defined in Claim 34 where in the compound employed (CH<sub>2</sub>)x is alkylene, alkenylene, allenyl, or alkynylene. --

## --10. (Amended) The method as defined in Claim 34 where in the compound employed



 A3 Cont aryloxycarbonyl, haloaryl-oxycarbonyl, alkoxyaryloxycarbonyl, alkylaryloxycarbonyl, arylalkenyloxycarbonyl, arylalkenyloxycarbonyl, cycloalkyloxyaryloxycarbonyl, alkyloxyaryloxycarbonyl, arylalkylsulfonyl, arylalkenylsulfonyl, arylthiocarbonyl, cycloheteroalkylalkyloxycarbonyl, cycloheteroalkylalkyloxycarbonyl,

--14. (Amended) The method as defined in Claim 34 where the compound employed has the structure



where  $(CH_2)_n$  is  $CH_2$  or  $CH_2$ . --

--16. (Amended) The method as defined in Claim 34 wherein the compound employed

has the structure



, where  $R^3 =$ 

$$\begin{array}{c|c} Ph \\ \hline \\ O \\ CH_3 \end{array}$$

$$\begin{array}{c} Ph \\ O \\ O \\ CH_3 \end{array}$$

$$\begin{array}{c} Ph \\ O \\ O \\ CH_3 \end{array}$$

$$\begin{array}{c} O \\ O \\ CO_2H \end{array}$$

$$\begin{array}{c} O \\ O \\ CH_3 \end{array}$$

$$\begin{array}{c} O \\ CO_2H \end{array}$$

$$\begin{array}{c} O \\ CO_2H \end{array}$$

$$\begin{array}{c} O \\ CH_3 \end{array}$$

Ph 
$$CO_2H$$
  $R^{3f}$  , where  $R^{3f}$  =

Ph 
$$O = S = R^{3g}$$
 $CO_2H$ , where  $R^{3g} = R^{3g}$ 

where R<sup>3g</sup> =

Ph 
$$CO_2H$$
  $CO_2H$  , where  $R^3 =$ 

wint-

Ph 
$$R^3$$
  $CO_2H$  where  $R^3 =$ 

Ph 
$$CO_2H$$
  $R^3$  , where  $R^3 =$ 

A Cont.

Ph—N—CO<sub>2</sub>H
$$CH_3$$

$$CH_3$$

$$CH_3$$

$$Where R^a = (\pm)-Me , (\pm) n-Bu ,$$

$$\begin{array}{c} \text{OCH}_3 \\ \text{Ph} \longrightarrow \text{OCH}_3 \\ \text{CH}_3 \times \text{CO}_2\text{H} \end{array}, \quad \begin{array}{c} \text{CH}_3 \\ \text{N} \longrightarrow \text{CO}_2\text{H} \\ \text{OCH}_3 \end{array}, \quad \begin{array}{c} \text{CH}_3 \\ \text{N} \longrightarrow \text{CO}_2\text{H} \\ \text{OCH}_3 \end{array}, \quad \begin{array}{c} \text{CH}_3 \\ \text{N} \longrightarrow \text{CO}_2\text{H} \\ \text{OCH}_3 \end{array}, \quad \begin{array}{c} \text{CH}_3 \\ \text{CH}_3 \end{array}, \quad \begin{array}{c} \text{CH}_3 \\ \text{CH}$$

$$\bigcirc CH_3 \\ \bigcirc CH_3 \\ \bigcirc CO_2H \\ \bigcirc CH_3 \\ \bigcirc CH_3 \\ \bigcirc CH_3$$

$$\begin{array}{c} \text{CH}_3 \\ \text{Ph} \\ \text{N} \\ \text{O} \\ \text{O}$$

OCH<sub>3</sub>

$$OCH_3$$

A)

--17. (Amended) The method as defined in Claim 34 wherein the compound employed has the structure

Coni.

$$\begin{array}{c} Ph \\ O \\ O \\ O \\ CH_3 \end{array}$$

$$\begin{array}{c} Ph \\ = N \\ CH_3 \end{array}$$

--18. (Amended) The method as defined in Claim 34 wherein the compound employed has the structure

--20. (Amended) The method as defined in Claim 34 wherein the compound employed

has the structure

A6

OCH₃

ĊO<sub>2</sub>H

ĊO<sub>2</sub>H

$$\begin{array}{c|c} & H_3C \\ & O \\ \hline \\ Ph \\ \hline \\ N \\ \hline \end{array}$$

$$Ph \xrightarrow{O \xrightarrow{CH_3}} O \xrightarrow{O \xrightarrow{O}} O \xrightarrow{O} O \xrightarrow{O} O$$

$$\begin{array}{c|c} CH_3 \\ \hline N \\ OCH_3 \\ \hline \end{array}$$

$$\begin{array}{c|c} O & CH_3 & N & CO_2H \\ \hline O & O & O \\ \hline O & O & O$$

$$Ar = CI \longrightarrow \bigcap_{i} F_3C \longrightarrow \bigcap_{i} F_3C$$

$$Ar \longrightarrow O \longrightarrow O \longrightarrow N \longrightarrow CO_2H$$

$$CH_3 \longrightarrow F_3C \longrightarrow F_3$$

--21. (Amended) The method as defined in Claim 55 wherein the compound employed has the structure

--22. (Amended) The method as defined in Claim 55 wherein the compound employed

Con.

or

--26. (Amended) The method as defined in Claim 55 wherein the compound employed has the structure



--27. (Amended) The method as defined in Claim 55 wherein the compound employed has the structure

Cons.

--28. (Amended) The method as defined in Claim 55 wherein the compound employed has the structure

--30. (Amended) The method as defined in Claim 55 wherein the compound employed has the structure



--31. (Amended) The method as defined in Claim 55 wherein the compound employed has the structure

As www.

--32. (Amended) The method as defined in Claim 55 wherein the compound employed has the structure

--34. (Amended) A method for lowering blood glucose levels or for treating diabetes, or for treating a premalignant disease, an early malignant disease, a malignant disease, or a dysplastic disease, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound which has the structure



$$R^{2a}$$
 $R^{2b}$ 
 $R^{2a}$ 
 $R$ 

wherein x is 1,2, 3 or 4; m is 1 or 2; n is 1 or 2;

Q is C or N;

A is O or S;

Z is O or a bond;

R1 is H or lower alkyl/

X is CH;

R<sup>2</sup> is H, alkyl, alkøxy, halogen, amino or substituted amino;

R<sup>2a</sup>, R<sup>2b</sup> and R<sup>2</sup> are the same or different and are selected from H, alkyl, alkoxy, halogen, amino or substituted amino;

R³ is aryloxycarbonyl, alkyloxycarbonyl, alkynyloxycarbonyl, alkynyloxycarbonyl, alkyloxycarbonyl, alkyloxycarbonyl, alkyloxycarbonyl, cycloalkylaryloxycarbonyl, cycloalkyloxyaryloxycarbonyl, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, alkylsulfonyl, alkoxycarbonyl, heteroaryloxycarbonyl, cycloheteroalkyloxycarbonyl, heteroarylakenyl, hydroxyalkyl, alkoxy, alkoxyaryloxycarbonyl, arylalkyloxycarbonyl, alkylaryloxycarbonyl,

Ag Com. alkynyloxycarbonyl, haloalkoxyaryloxycarbonyl, alkoxycarbonylaryloxycarbonyl, aryloxyaryloxycarbonyl, arylalkenyloxycarbonyl, heteroaryloxyarylalkyl, aryloxyarylalkyloxycarbonyl, arylalkyloxycarbonyl, arylalkenylsulfonyl, heteroarylalkyloxycarbonyl, heteroarylalkyloxyarylalkyl, arylalkenylarylalkyl, arylalkenylarylalkyl, arylalkoxycarbonylheteroarylalkyl, heteroaryloxyarylalkyl, arylalkenylheteroarylalkyl or polyhaloalkylaryloxycarbonyl;

Y is CO<sub>2</sub>R<sup>4</sup> where R<sup>4</sup> is H or alkyl, or a prodrug ester or Y is a C-linked 1-tetrazole, a phosphinic acid of the structure P(O)(OR<sup>4a</sup>)R<sup>5</sup> where R<sup>4a</sup> is H or a prodrug ester, R<sup>5</sup> is alkyl or aryl or a phosphonic acid of the structure P(O)(OR<sup>4a</sup>)<sub>2</sub> where R<sup>4a</sup> is H or a prodrug ester;

or stereoisomers thereof, prodrug esters thereof, and pharmaceutically acceptable salts thereof. --

--37.(Amended) A pharmaceutical combination comprising a compound which has the structure



wherein x is 1,2, 3 or 4; m is 1 or 2; n is 1 or 2;

Q is C or N;

A is O or S;

Z is O or a bond;

R<sup>1</sup> is H or lower alkyl;

X is CH;

R<sup>2</sup> is H, alkyl, alkoxy, halogen, amino or substituted amino;

R<sup>2a</sup>, R<sup>2b</sup> and R<sup>2c</sup> are the same or different and are selected from H, alkyl, alkoxy, halogen, amino or substituted amino;

R³ is aryloxycarbonyl, alkyloxycarbonyl, alkynyloxycarbonyl, alkenyloxycarbonyl, alkyl(halo)aryloxycarbonyl, alkyloxy(halo)aryloxycarbonyl, cycloalkylaryloxycarbonyl, cycloalkyloxyaryloxycarbonyl, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, alkoxycarbonylamino, aryloxycarbonylamino, heteroaryloxycarbonyl, alkylsulfonyl, alkenylsulfonyl, heteroaryloxycarbonyl, cycloheteroalkyloxycarbonyl, heteroarylalkenyl, hydroxyalkyl, alkoxy, alkoxyaryloxycarbonyl, arylalkyloxycarbonyl, alkylaryloxycarbonyl,

alkynyloxycarbonyl, haloalkoxyaryloxycarbonyl, alkoxycarbonylaryloxycarbonyl, aryloxyaryloxycarbonyl, arylalkenyloxycarbonyl, heteroaryloxyarylalkyl, aryloxyarylalkyloxycarbonyl, arylalkyloxycarbonyl, arylalkyloxycarbonyl, arylalkenylsulfonyl, heteroarylalkyloxyarylalkyl, arylalkenylarylalkyl, arylalkenylarylalkyl, arylalkoxycarbonylheteroarylalkyl, heteroaryloxyarylalkyl, arylalkenylheteroarylalkyl or polyhaloalkylaryloxycarbonyl;

All Con.

Y is  $CO_2R^4$  where  $R^4$  is H or alkyl, or a prodrug ester or Y is a C-linked 1-tetrazole, a phosphinic acid of the structure  $P(O)(OR^{4a})R^5$  where  $R^{4a}$  is H or a prodrug ester,  $R^5$  is alkyl or aryl or a phosphonic acid of the structure  $P(O)(OR^{4a})_2$  where  $R^{4a}$  is H or a prodrug ester;

or stereoisomers thereof, prodrug esters thereof, and pharmaceutically acceptable salts thereof, and a lipid-lowering agent, a lipid modulating agent, an antidiabetic agent, an anti-obesity agent, an antihypertensive agent, a platelet aggregation inhibitor, and/or an antiosteoporosis agent. ---

--39. (Amended) The combination as defined in Claim 37 wherein the antidiabetic agent is 1, 2, 3 or more of a biguanide, a sulfonyl urea, a glucosidase inhibitor, a PPAR $\alpha$  agonist, a PPAR  $\alpha$ /γ dual agonist, an SGLT2 inhibitor, a DP4 inhibitor, an aP2 inhibitor, an insulin sensitizer, a glucagon-like peptide-l (GLP-l), insulin and/or a meglitinide; the anti-obesity agent is a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, a thyroid receptor agonist, an aP2 inhibitor and/or an anorectic agent; the lipid lowering agent is an MTP inhibitor, an HMG CoA reductase inhibitor, a squalene synthetase inhibitor, a fibric acid derivative, an upregulator of LDL receptor activity, a lipoxygenase inhibitor, or an ACAT inhibitor; the antihypertensive agent is an ACE inhibitor, angiotensin II receptor antagonist, NEP/ACE inhibitor, calcium channel blocker and/or  $\beta$ -adrenergic blocker. --

--40. (Amended) The combination as defined in Claim 39 wherein the antidiabetic agent is 1, 2, 3 or more of metformin, glyburide, glimepiride, glipyride, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin, Gl-262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide, KAD1129, AR-HO39242, GW-409544, KRP297, AC2993, LY315902, P32/98 and/or NVP-DPP-728A; the anti-obesity agent is orlistat, ATL-962, AJ9677, L750355, CP331648, sibutramine, topiramate, axokine, dexamphetamine, phentermine, phenylpropanolamine, and/or mazindol; the



lipid lowering agent is pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin,

Cont

itavastatin, visastatin, fenofibrate, gemfibrozil, clofibrate, avasimibe, TS-962, MD-700, cholestagel, niacin and/or LY295427; the antihypertensive agent is an ACE inhibitor which is captopril, fosinopril, enalapril, lisinopril, quinapril, benazepril, fentiapril, ramipril or moexipril; an NEP/ACE inhibitor which is omapatrilat, [S[(R\*,R\*)]-hexahydro-6-[(2-mercapto-1-oxo-3-phenylpropyl)amino]-2,2-dimethyl-7-oxo-1H-azepine-1-acetic acid (gemopatrilat) or CGS 30440;

an angiotensin II receptor antagonist which is irbesartan, losartan or valsartan; amlodipine besylate, prazosin HCl, verapamil, nifedipine, nadolol, propranolol, carvedilol, or clonidine HCl; the platelet aggregation inhibitor is aspirin, clopidogrel, ticlopidine, dipyridamole or ifetroban. --

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--50. (Amended) A method for treating insulin resistance, hyperglycemia, hyperinsulinemia, or elevated blood levels of free fatty acids or glycerol, hyperlipidemia, obesity, Syndrome X, dysmetabolic syndrome, inflammation, diabetic complications, impaired glucose homeostasis, impaired glucose tolerance, hypertriglyceridemia, atherosclerosis, or for treating irritable bowel syndrome, Crohn's disease, gastric ulceritis or osteroporosis, or psoriasis, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a pharmaceutical combination as defined in Claim 37. --

Please add the following Claims 55 and 56.



55. A method for lowering blood glucose levels or for treating diabetes, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound which has the structure

$$\begin{array}{c|c} & & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & \\ & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & &$$

where  $R^1$  is alkyl,  $\begin{array}{c} CH_3 \\ (CH_2)_m \text{ is } CH_2 \text{ or } \end{array}$  and  $R^3$  is aryloxycarbonyl or alkoxyaryloxycarbonyl.